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Supplementary Materials for

Uncovering the biological basis of control energy: Structural and metabolic correlates of energy inefficiency in temporal lobe epilepsy

Xiaosong He *et al.*

Corresponding author: Xiaosong He, hexs@ustc.edu.cn; Dani S. Bassett, dsb@seas.upenn.edu

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Supplementary Methods

S1: Methodological consideration on intrinsic connectivity network (ICN) defined brain states

A "brain state", or an activation state mentioned in this and other studies (*9*, *10*, *13*, *16*), refers to a pattern of brain activity that can be coded as a vector of activity magnitudes across all brain regions. All brain regions will be active to a certain extent all the time; however, some will be more active than others during distinct cognitive tasks. The pattern of activation characteristic of a cognitive task is sometimes also referred to as the pattern of co-activation, to highlight the interesting dependence in activity between region pairs (*35*, *92–94*). For example, during a working memory task, we can decompose the dynamic neural processes—from viewing a stimulus to pressing a button—into several brain states. When the subject views the stimulus, regions within the visual cortex are co-activated more than the rest of the brain; afterwards, activations in fronto-parietal regions become dominant, as these specifically subserve working memory; lastly, the motor system becomes more active to drive the button response. In each of these phases, a distinct system of brain regions (*i.e.*, an ICN) is predominantly active, while the rest of the brain is relatively less active, as can be observed via fMRI (*95*).

Accordingly, our simulation mimics the transition from one brain state when a particular ICN is most active, to another brain state in which another ICN is most active, as an approximation of transitions between the empirically observed co-activation patterns (*35*, *92–94*). Transitions between co-activation patterns characterized by selectively activated brain networks are commonly observed in fMRI studies. In our previous fMRI study (*2*), we used a clustering algorithm to show that transitions between representative co-activation patterns occur during both rest and an N-back working memory task. These transitions are influenced by task demands and meaningfully related to individual differences in behavior. Further, simulations showed that the control energy needed to facilitate such transitions is associated with chronological age (*2*). Using similar techniques, results from another group indicated that transitions between representative co-activation patterns are associated with cognitive performance in the presence of pathology (*96*). Such transitions can even be observed in fMRI studies performed on animal models, and are related to distinct levels of consciousness in the mouse brain (*97*).

In our study, the ICNs used to represent such co-activation patterns were obtained from an established parcellation of the brain into cognitive systems (*38*). It has been demonstrated that, regions belonging to such systems do not only co-synchronize during rest (*37*, *38*), but also co-activate during different cognitive conditions (*37*, *39*, *40*). Using a mathematical simplification, we can further binarize these ICN-defined co-activation patterns by setting those regions that are relatively more active (*i.e.*, regions within a specific ICN) to 1, and those that are relatively less active (*i.e.*, the rest of the brain) to 0. In so doing, we consider activity in the less active regions as a mean-centered baseline, and the activity in the more active regions to be greater than that baseline by 1 arbitrary unit. This setting is analogous to

task fMRI analyses, where contrasts are commonly set between a condition of interest (1) and a baseline condition (0) (see *Ref.* (*16*)).

We have previously deployed such binarized ICNs as forms of simplified co-activation patterns in several studies (*9*, *10*, *13*, *16*). Some previous studies have laid out the biological relevance of control energy estimated using binary brain states. For example, in one study, we demonstrated that variance in the control energy needed to attain a binary brain state centered on the frontal-parietal network was associated with executive function development in youth (*16*). Another independent group also adopted a similar strategy and found that the control energy needed to transition from a binary brain state centered on the DMN to another centered on the motor network was associated with aging (*98*). Importantly, consistent results have been reported even when random noise is introduced into the binary brain state, providing additional support to these observations (*16*).

In reality, there are many intermediate states when a partial ICN, or two or more ICNs, are active at the same time. Importantly, the linear nature of our NCT model permits us to write any transitions between any pair of such intermediate states in the form of linear combinations of transitions between single ICNs (*9*). Hence, we explored the average energy cost during simulated transitions among all the ICNs so that transitions between intermediate states could be simulated in the same process. This intuition is further verified, when we tested the average energy cost during simulated transitions among non-binary random brain states in which every region is activated at a random magnitude, and found almost identical results.

While this functional parcellation of ICNs has been derived from healthy subjects, it has recently been broadly applied to clinical populations, including epilepsy patients, to quantify the functional integrity of major cognitive systems. For example, this functional parcellation is frequently used to identify stratifying effects at the functional network level, *e.g.*, for cortical atrophy patterns (*99*) and atypical functional connectome hierarchy (*100*) in TLE, disrupted functional gradients of the cortical connectome both in TLE (*101*) and generalized epilepsies (*102*), as well as associations between altered communication dynamics and cognitive deficits in TLE (*34*). This functional parcellation has also been used to localize large-scale functional networks within which the rapid spread of ictal activity arises (*103*), and to identify altered functional connectivity patterns important for epilepsy classification (*104*). Further, this functional parcellation provides the field map that has been used to quantify thalamocortical functional connectivity organization in TLE and generalized epilepsies (*46*, *105*). Collectively, these past studies underscore the fact that this functional parcellation has substantially advanced our understanding of the pathological impacts of epilepsy on the functional organization of the brain.

Nonetheless, it is possible that TLE patients may present with atypical patterns of region allocation to large-scale functional networks. However, our approach to use generic ICNs detected previously was motivated by our goal to isolate the dynamical consequences of abnormal structural network topology; if we had used distinct ICNs for the two groups, our

results would have conflated the structural network mechanism with the separate mechanism of differences in brain states. Thus, employing different ICNs between groups would confound our interpretation of the control energy findings. Instead, by setting uniform brain states for patients and controls, we ensured comparability of control energy across groups. In a future study, it would be of interest to develop and rigorously validate a new methodological approach (and associated statistical inference methods) that would allow investigators to separately quantify the contributions of structural connectivity and distinct brain states on the estimated control energy in the context of group comparisons.

Taken together, ICN-defined binary brain states can be a useful tool in network control theory (NCT) studies. Importantly, our data and extensive prior studies underscore that this state transition framework can be used as a simple approximation of the empirical brain dynamics commonly observed via fMRI. In specific, by adopting the public functional parcellation of cognitive systems (*i.e.*, ICNs) to define brain states in our study, we directly isolate the structural effects of interest while simultaneously ensuring a clean comparison with previous studies.

Supplementary Results

S1: Sensitivity Analyses on the impact of overall white matter health

In this section, we evaluated the impact of overall white matter health on our results reported in the main text. White matter lesions are commonly detected with specific T2-weighted imaging sequences in the form of white matter hyperintensity (WMH). In the absence of such data, here, we estimated global WMH volume with T1-weighted image using the Computational Anatomy Toolbox (CAT12). To evaluate the robustness of our original findings, we extracted estimates of WMH for each subject and regressed those estimates out of our control energy metrics. We then repeated our main analyses, and found consistent results at every step.

In specific, we found that temporal lobe epilepsy (TLE) patients required greater global optimal control energy (OCE) to activate the limbic network compared to healthy controls (HCs, Welch's t_{108}=3.80, P_{corr}=0.002). The global OCE needed to activate other intrinsic connectivity networks (ICNs) did not significantly differ between the two groups (Welch's $|t_{108}$'s$|$<1.51, P_{corr}>0.642). When we simulated the activation of left and right limbic ICN separately, we found again a significant hemisphere-by-group interaction [$F_{(2,107)}$=10.76, P=6×10^{-5}]. When comparing regional energy efficiency in supporting cross-ICN transitions, we found significantly elevated control energy consumption in TLE in the ipsilateral temporal pole (t_{59}=4.89, P_{corr}=0.001), inferior temporal gyrus (t_{59}=4.71, P_{corr}=0.002), amygdala (t_{59}=5.15, P_{corr}=3×10^{-4}), hippocampus (t_{59}=4.87, P_{corr}=0.001), parahippocampal gyrus (t_{59}=4.26, P_{corr}=0.008), fusiform gyrus (t_{59}=4.86, P_{corr}=0.001), and the isthmus of the cingulate gyrus (t_{59}=4.09, P_{corr}=0.014). Similar results were found for transitions between random states at the ipsilateral temporal pole (t_{59}=4.29, P_{corr}=0.007), inferior temporal gyrus (t_{59}=4.33, P_{corr}=0.006), amygdala (t_{59}=3.49, P_{corr}=0.091), hippocampus (t_{59}=4.25, P_{corr}=0.009), parahippocampal gyrus (t_{59}=5.16, P_{corr}=3×10^{-4}), fusiform gyrus (t_{59}=5.12, P_{corr}=4×10^{-4}), and isthmus of the cingulate gyrus (t_{59}=4.75, P_{corr}=0.001). When we tested associations between the LIs of control energy and glucose metabolism, we found significant correlations between the LIs at the amygdala (R_{49}=-0.63, P_{corr}=6×10^{-6}), hippocampus (R_{49}=-0.60, P_{corr}=3×10^{-5}), parahippocampal gyrus (R_{49}=-0.49, P_{corr}=0.002), and fusiform gyrus (R_{49}=-0.39, P_{corr}=0.034), marginally at the temporal pole (R_{49}=-0.35, P_{corr}=0.075), but not within the inferior temporal gyrus (R_{49}=-0.34, P_{corr}=0.103) or isthmus of cingulate gyrus (R_{49}=-0.22, P_{corr}=0.587). These results are highly consistent with our main findings, hence can support all the original conclusions in the main text. Therefore, changes to control energy metrics are mainly driven by changes to the dynamics occurring atop altered structural networks rather than being driven by overall white matter health.

S2. Sensitivity analyses on the comparison between control energy and conventional descriptive connectomic metrics

Conventional descriptive connecctomic metrics, such as nodal degree and strength, can also provide information regarding local topology of the structural network. Accordingly, they may share similar cross-subject variances embedded in our control energy metrics. To provide further discrimination between these two types of metrics, in this section, we explored whether similar results can be produced with such conventional derivatives of the structural connectome, and whether control energy can provide unique information compared to them.

We began by replacing global OCE needed to activate each ICN with the connectivity strength of each ICN (*i.e.*, sum of all edge weights connected to all regions within each ICN respectively), and compared the latter between TLE patients and HCs as we had in Figure 2 in the main text. Such network connectivity strength is an analog to nodal strength, but at the network level. Consistent with our control energy analyses, we first regressed out the same confounding factors used in the main text. We then conducted a permutation-based *t*-test on the so-obtained residuals, using the same approach as in our main analyses. Patients with TLE had lower limbic connectivity strength compared to HCs (Welch's t_{108}=-3.24, P_{corr}=0.013). The connectivity strength of other ICNs, however, did not significantly differ between groups (Welch's $|t_{108}$'s$|$<1.48, P_{corr}>0.661). These results confirm that limbic changes in control energy in TLE are paralleled by changes in connectivity strength, as expected based on the mathematical derivation of control energy metrics. We then assessed the specific contributions of limbic control energy and limbic connectivity strength in differentiating patients and HCs. We devised a logistic regression model using group as a binary dependent variable (HC or patient with TLE), and both limbic control energy and limbic connectivity strength as independent variables, entered in a stepwise fashion. Interestingly, control energy alone (β=3.884, t=3.437, P=5.9×10^{-4}) was selected in the final model (Nagelkerke R^2=0.160, χ^2=14.016, P=1.8×10^{-4}), while connectivity strength was not included in the model, as it was not significant (P=0.483). This result suggests that control energy is more sensitive in highlighting difference between patients and HCs, rather than redundant.

Next, we replaced nodal minimal control energy (MCE) with nodal degree and strength, respectively, and performed the same statistical analyses as those presented in Figures 4 and 5 in the main text. Consistent with our control energy analyses, we first regressed out the same confounding factors used in the main text. We then conducted permutation-based analyses on the so-obtained residuals, using the same approach as in our main analyses.

1) We first probed group differences in nodal degree. Compared to controls, patients with TLE presented with greater degree in the ipsilateral putamen (t_{59}=4.80, P_{corr}=8×10^{-4}) and lesser degree in the contralateral nucleus accumbens (t_{59}=-3.92, P_{corr}=0.019), but not in any of the ipsilateral temporo-limbic regions. The latter findings differ from our control energy findings (**Table S2**). We then used nodal degree as a nuisance covariate in all group comparisons of nodal control energy. These sensitivity analyses yielded virtually identical results to those of our

original analyses, as detailed in **Table S2**. Taken together, our findings demonstrate that the energetic differences between patients with TLE and controls was not driven by degree.

2) Next, we considered nodal strength. Comparison of patients and controls highlighted lesser nodal strength in TLE patients, consistent with our control energy findings (**Table S3**). In all group comparisons of nodal control energy, we then covaried for nodal strength, and found that results were partially consistent with our original analysis. Specifically, we found group differences in control energy within the hippocampus, inferior temporal gyrus and fusiform gyrus that met the threshold for corrected significance (**Table S3)**. Thus, while nodal strength is relevant to intergroup differences, it is not sufficient to fully account for our control energy findings.

3) Next, we tested associations of the laterality indices (LIs) of nodal degree and strength with glucose metabolism. Among the aforementioned regions in Tables S2 and S3, the LIs of nodal degree and glucose metabolism were not significantly correlated ($|R_{49}|<0.23$, $P_{corr}>0.534$). There were, however, significant correlations between LIs of glucose metabolism and nodal strength, which paralleled our findings of correlation analyses with control energy. Accordingly, we regressed out nodal strength from control energy, and re-estimated the associations between the LIs of glucose metabolism and control energy, and were able to largely replicate the correlational results reported in our main analyses, as detailed in **Table S4**.

4) Lastly, we evaluated whether the LI of control energy more accurately predicts the LI of glucose metabolism than the LI of nodal strength. For each of the above regions, we constructed a stepwise logistic regression model using the LI of glucose metabolism as the dependent variable, and both the LIs of control energy and nodal strength as independent variables. The results confirmed that control energy is a significant predictor of metabolic laterality, and suggested that strength and control energy may exhibit unique and, at times, complementary predictive power (**Table S5**). Specifically, in temporal pole and amygdala, the LI of control energy was the only successful predictor of metabolic LI. In the hippocampus and fusiform gyrus, both the LIs of control energy and nodal strength contributed to the prediction of metabolic LI; for the hippocampus, *beta* values and *t*-statistics were higher for control energy than for strength. For the parahippocampal gyrus only, the LI of control energy was originally significant, but was then excluded by the model due to its high collinearity with the LI of nodal strength (VIF=3.327).

Taken together, these extensive sensitivity analyses indicate that control energy is not a redundant metric, and cannot be entirely explained by conventional descriptive connectomic metrics. Furthermore, all of our analyses demonstrate that control energy generally confers superior explanatory power compared to canonical nodal graph theoretical metrics.

S3. Sensitivity analyses on the comparison between control energy and controllability

Controllability metrics, such as average and modal controllability, are the first NCT metrics brought into neuroscientific inquires to describe the general ability of each region to control neural dynamics depending upon the full topology of the structural network (*13*). Controllability metrics and the control energy metrics used in this study are a family of internally-consistent metrics all derived from the same simplified noise-free linear and time-invariant model of network dynamics depicted in *Eq.* 1. They differ in that each summarizes a distinct aspect of that model applied in different contexts. The term *controllability* describes the general ability of each region to control neural dynamics depending upon the full topology of the structural network (*13*), and it is estimated in the scenario of controlling whole-brain network dynamics from a single region to achieve all possible brain state transitions (*8*). Importantly, controllability can be quantified by the infinite impulse response (average controllability) or the eigenvalues (modal controllability) of the A matrix; both quantifications assess all possible states, and if one instead wishes to model a specific transition between a single pair of states or a small number of states, then one needs a different metric (*13*). In this case, the metric of control energy becomes useful as it summarizes the control inputs $u(t)$ over a finite period of a simulated dynamic transition between two specific brain states. The control energy metric not only depends on the topology of the A matrix, but also on the specific time horizon ($0 \rightarrow T$), distance between the initial and final states ($x(T) - x(0)$), and the transition trajectory, as well as the location and number of nodes that are under control. In our study, we let all the brain regions to be controllable, which is more biologically plausible than controlling from a single region. The optimal control framework allows us to estimate the minimal energy costs to facilitate the designated brain state transitions while following the shortest trajectory. The approach relies on a key modeling assumption: that the brain operates as an efficient system that minimizes the expenditure of energy and the distance the system can traverse in state space. In Simulation II of our study, we pursued a hybrid approach in which we aimed to approximate all possible brain state transitions without constraining the trajectory length; this hybrid approach is made possible by the minimal control framework which allows the brain to move more freely across different intermediate states. As these descriptions and comparisons demonstrate, in contrast to the controllability metrics the control energy approach allows us to more flexibly model and describe the neural dynamics under specific state transition scenarios.

To further probe the distinctions between these NCT metrics at describing regional energetic efficiency, in this section, we first evaluated their associations, then test whether similar findings can be produced with average and modal controllability, and whether control energy can provide unique information compared to them.

In the main text, MCE during cross-ICN transitions was used to describe regional energetic efficiency. Accordingly, here we correlated the estimated MCE with both average and modal controllability across all regions in each subject to test whether these measures are inter-changeable. After correction for multiple comparisons, only 6 out of the 110 participants

demonstrated significant correlations between MCE and modal controllability, while none of them showed significant correlations between MCE and average controllability. Therefore, while the interpretation of the MCE can be analogous to controllability, these distinctions are more or less expected given the quite different factors these metrics are constructed to track and reflect. Nonetheless, they can still share cross-subject variances in our group-level analyses. We thus explored whether, after replacing control energy with controllability, we could reproduce results indicating that these NCT measures relate to brain metabolism. Consistent with our control energy analyses, we first regressed out the same confounding factors used in the main text. We then conducted permutation-based analyses on the so-obtained residuals, using the same approach as in our main analyses. We outline these sensitivity analyses below.

1) Compared to HCs, TLE patients had lower average controllability (**Table S6**) and greater modal controllability (**Table 7**), which largely paralleled our primary control energy findings. After regressing out either average or modal controllability before group comparisons of nodal control energy, we obtained results that were largely similar to those of our main analysis, as detailed in **Tables S6 and S7**.

2) When we tested the associations between LIs of glucose metabolism and average controllability among the aforementioned regions, we did not find any significant results ($|R_{49}|<0.33$, $P_{corr}>0.136$). Notably, we found significant correlations between the LIs of glucose metabolism and modal controllability, which were similar to our findings in control energy. After regressing out modal controllability and then re-estimating associations between the LIs of glucose metabolism and control energy, we also largely reproduced the findings of our main analysis, as detailed in **Table S8**. Taken together, these results suggest that similar to control energy, modal controllability also relates to brain metabolism. However, the association between control energy and glucose metabolism cannot be fully accounted for by the association between modal controllability and glucose metabolism.

3) Lastly, we tested whether control energy better tracks the relationship between energetic efficiency and glucose metabolism, compared to modal controllability. For each of our regions of interest (see main text and **Table S8**), we formulated a stepwise logistic regression model using the LI of glucose metabolism as the dependent variable, and both LIs of control energy and modal controllability as independent variables. For the temporal pole, amygdala, and parahippocampal gyrus, the LI of control energy was the identified as the exclusive predictor of the LI of glucose metabolism. For the hippocampus and fusiform gyrus, both LIs of control energy and modal controllability comparably contributed to predicting the LI of glucose metabolism. Only in the inferior temporal gyrus, the LI of modal controllability was the exclusive predictor of LI of glucose metabolism. These results are shown in **Table S9**.

In summary, controllability metrics, especially modal controllability can be used to largely reproduce the results to support our main claims, *i.e.*, that energy efficiency estimated via NCT is associated with brain metabolism as tracked by PET. Nonetheless, control energy is more

sensitive to the effects of pathology (*i.e.*, differences between patients and controls) and is a better predictor of regional brain metabolism compared to controllability.

Table S1. Permutation-based nonparametric one-sample *t*-tests on laterality indices (LIs) of regional glucose uptake reveal significant ipsilateral hypometabolism in temporal lobe epilepsy patients.

Lausanne Atlas Region Label	LI (mean±std)	t_{49}	P_{corr}	Cohen's *d*
lateralorbitofrontal_1	-0.014±0.019	-5.383	1×10^{-4}	-0.761
rostralmiddlefrontal_1	-0.005±0.01	-3.678	0.023	-0.520
superiorfrontal_3	-0.007±0.013	-3.622	0.027	-0.512
isthmuscingulate_1	-0.016±0.02	-5.788	3×10^{-5}	-0.819
supramarginal_1	-0.014±0.024	-4.226	0.005	-0.598
superiorparietal_2	-0.011±0.017	-4.492	0.002	-0.635
inferiorparietal_1	-0.013±0.019	-4.690	0.001	-0.663
precuneus_2	-0.017±0.036	-3.401	0.049	-0.481
lateraloccipital_2	-0.011±0.019	-3.908	0.012	-0.553
fusiform_2	-0.016±0.019	-6.196	1×10^{-5}	-0.876
parahippocampal_1	-0.018±0.021	-5.981	2×10^{-5}	-0.846
entorhinal_1	-0.039±0.042	-6.652	5×10^{-6}	-0.941
temporalpole_1	-0.045±0.049	-6.608	5×10^{-6}	-0.935
inferiortemporal_1	-0.024±0.03	-5.695	4×10^{-5}	-0.805
inferiortemporal_2	-0.013±0.017	-5.452	1×10^{-4}	-0.771
middletemporal_1	-0.012±0.02	-4.191	0.005	-0.593
middletemporal_2	-0.026±0.027	-6.795	2×10^{-6}	-0.961
bankssts_1	-0.02±0.023	-6.245	1×10^{-5}	-0.883
superiortemporal_1	-0.014±0.02	-4.742	0.001	-0.671
insula_1	-0.024±0.039	-4.485	0.002	-0.634
thalamusproper	-0.008±0.013	-4.228	0.005	-0.598
putamen	-0.005±0.008	-4.830	0.001	-0.683
pallidum	-0.013±0.021	-4.422	0.003	-0.625
accumbensarea	-0.008±0.015	-3.746	0.019	-0.530
hippocampus	-0.026±0.026	-7.173	1×10^{-6}	-1.014
amygdala	-0.028±0.031	-6.423	9×10^{-6}	-0.908

* The LI is calculated as $\boldsymbol{LI_i = \frac{Ipsilateral_i - Contralateral_i}{Ipsilateral_i + Contralateral_i}}$, whereas a negative LI indicated lower ipsilateral compared to contralateral metabolism. Only regions with LIs significantly different from zero after multiple comparisons corrections are presented. Statistics including the *t*-value, corrected *P*-value (P_{corr}), and effect size (Cohen's *d*) are depicted. The regions co-exhibiting ipsilateral abnormalities in energy profiles are highlighted in bold.

Table S2 shows statistics pertaining to comparisons of deviation scores (against data from healthy controls) of control energy and nodal degree, which were determined by a permutation-based one sample *t*-test. P_{corr}, *P* values were corrected for multiple comparisons by controlling the family-wise error rate.

Ipsilateral regions	Control Energy (original results)		Degree		Control Energy (covaried for Degree)	
	t	P_{corr}	*t*	P_{corr}	*t*	P_{corr}
Temporal Pole	5.40	1×10^{-4}	-1.88	0.985	5.15	3×10^{-4}
Inferior Temporal	5.03	5×10^{-4}	-0.52	1	5.52	9×10^{-5}
Amygdala	6.01	1×10^{-5}	-2.13	0.917	5.84	3×10^{-5}
Hippocampus	5.24	2×10^{-4}	-1.71	0.997	5.48	1×10^{-4}
Parahippocampal	4.54	0.003	-2.03	0.955	4.45	0.004
Fusiform	4.93	7×10^{-4}	-3.45	0.086	5.79	3×10^{-5}
Isthmus of Cingulate	4.17	0.011	2.16	0.905	4.02	0.018

Table S3 shows statistics pertaining to comparisons of deviation scores (against data from healthy controls) of control energy and nodal strength, which were determine by a permutation-based one sample *t*-test. P_{corr}, *P* values were corrected for multiple comparisons by controlling the family-wise error rate; P_{unc}, uncorrected *P* values for reference only.

Ipsilateral regions	Control Energy (original results)		Strength		Control Energy (covaried for Strength)	
	t	P_{corr}	*t*	P_{corr}	*t*	P_{unc}/P_{corr}
Temporal Pole	5.40	1×10^{-4}	-4.39	0.005	2.53	0.014/0.719
Inferior Temporal	5.03	5×10^{-4}	-4.89	0.001	5.43	$1\times10^{-6}/1\times10^{-4}$
Amygdala	6.01	1×10^{-5}	-4.10	0.015	3.12	0.003/0.241
Hippocampus	5.24	2×10^{-4}	-4.23	0.009	4.01	2×10^{-4}/0.018
Parahippocampal	4.54	0.003	-5.03	5×10^{-4}	2.32	0.024/0.876
Fusiform	4.93	7×10^{-4}	-5.52	9×10^{-5}	5.24	$2\times10^{-6}/2\times10^{-4}$
Isthmus of Cingulate	4.17	0.011	-5.62	6×10^{-5}	0.76	0.453/1

Table S4 Associations between LIs of glucose metabolism with nodal strength and control energy (with and without regressing out nodal strength), that were determined by a permutation-based product-moment correlation; P_{corr}, P values were corrected for multiple comparisons by controlling the family-wise error rate.

Ipsilateral regions	Control Energy (original results)		Strength		Control Energy (covaried for Strength)	
	R	P_{corr}	R	P_{corr}	R	P_{corr}
Temporal Pole	-0.37	0.049	0.22	0.602	-0.39	0.034
Inferior Temporal	-0.34	0.096	0.59	5×10^{-5}	-0.32	0.143
Amygdala	-0.62	8×10^{-6}	0.41	0.023	-0.52	0.001
Hippocampus	-0.60	3×10^{-5}	0.54	3×10^{-4}	-0.46	0.005
Parahippocampal	-0.50	0.002	0.60	3×10^{-5}	-0.36	0.066
Fusiform	-0.39	0.036	0.45	0.007	-0.33	0.108
Isthmus of Cingulate	-0.22	0.551	0.21	0.668	-0.03	1

Table S5 Stepwise linear regression models revealing the contributions of the LIs of control energy (CE) and nodal strength (Str) in predicting the LI of glucose metabolism (Glu). β values presented here are standardized coefficients.

LI of:	Final model	Statistics for the final model	Statistics for each independent variable
Temporal Pole	Glu ~ β_1×CE	R^2=0.140, F(1,48)=7.810, P=0.007	β_1=-0.374, t=-2.795, P=0.007, VIF=1
Inferior Temporal	Glu ~ β_1×Str	R^2=0.347, F(1,48)=25.457, P=7×10^{-6}	β_1=0.589, t=5.046, P=7×10^{-6}, VIF=1
Amygdala	Glu ~ β_1×CE	R^2=0.385, F(1,48)=29.990, P=2×10^{-6}	β_1=-0.620, t=-5.476, P=2×10^{-6}, VIF=1
Hippocampus	Glu ~ β_1×CE+β_2×Str	R^2=0.440, F(2,47)=18.483, P=1×10^{-6}	β_1=-0.436, t=-3.499, P=0.001, VIF=1.305 β_2=0.332, t=2.660, P=0.011, VIF=1.305
Parahippocampal	Glu ~ β_1×Str	R^2=0.363, F(1,48)=27.409, P=4×10^{-6}	β_1=0.603, t=5.235, P=4×10^{-6}, VIF=1
Fusiform	Glu ~ β_1×CE+β_2×Str	R^2=0.333, F(2,47)=11.743, P=7×10^{-5}	β_1=-0.363, t=-3.046, P=0.004, VIF=1.003 β_2=0.428, t=3.589, P=0.001, VIF=1.003
Isthmus of Cingulate	No variable entered.		

Table S6 shows statistics pertaining to comparisons of deviation scores (against data from healthy controls) of control energy and average controllability, which were determined by a permutation-based one sample *t*-test. P_{corr}, *P* values were corrected for multiple comparisons by controlling the family-wise error rate.

Ipsilateral regions	Control Energy (original results)		Average Controllability		Control Energy (covaried for Av. Control)	
	t	P_{corr}	*t*	P_{corr}	*t*	P_{corr}
Temporal Pole	5.40	1×10^{-4}	-1.39	1	5.29	2×10^{-4}
Inferior Temporal	5.03	5×10^{-4}	-6.12	5×10^{-6}	6.10	7×10^{-6}
Amygdala	6.01	1×10^{-5}	-2.08	0.869	5.95	1×10^{-5}
Hippocampus	5.24	2×10^{-4}	-6.90	1×10^{-6}	4.14	0.012
Parahippocampal	4.54	0.003	-5.49	5×10^{-5}	3.78	0.039
Fusiform	4.93	7×10^{-4}	-5.83	1×10^{-5}	5.43	1×10^{-4}
Isthmus of Cingulate	4.17	0.011	-6.37	2×10^{-6}	2.64	0.632

Table S7 shows statistics pertaining to comparisons of deviation scores (against data from healthy controls) of control energy and modal controllability, which were determined by a permutation-based one sample *t*-test. P_{corr}, *P* values were corrected for multiple comparisons by controlling the family-wise error rate; P_{unc}, uncorrected *P* values for reference only.

Ipsilateral regions	Control Energy (original results)		Modal Controllability		Control Energy (covaried for Mod. Control)	
	t	P_{corr}	*t*	P_{corr}	*t*	P_{unc}/P_{corr}
Temporal Pole	5.40	1×10^{-4}	4.31	0.005	2.97	0.004/0.355
Inferior Temporal	5.03	5×10^{-4}	4.14	0.009	4.86	1×10^{-5}/0.001
Amygdala	6.01	1×10^{-5}	3.75	0.035	4.84	1×10^{-5}/0.001
Hippocampus	5.24	2×10^{-4}	5.02	4×10^{-4}	3.73	4×10^{-4}/ 0.045
Parahippocampal	4.54	0.003	3.57	0.062	2.70	0.009/0.596
Fusiform	4.93	7×10^{-4}	3.12	0.224	5.04	$5\times10^{-6}/5\times10^{-4}$
Isthmus of Cingulate	4.17	0.011	3.94	0.018	1.84	0.071/1

Table S8 Associations between the LIs of glucose metabolism with modal controllability and control energy (with and without regressing out modal controllability), which were determined by a permutation-based product-moment correlation. P_{corr}, P values were corrected for multiple comparisons by controlling the family-wise error rate.

Ipsilateral regions	Control Energy (original results)		Modal Controllability		Control Energy (covaried for Mod. Control)	
	R	P_{corr}	R	P_{corr}	R	P_{corr}
Temporal Pole	-0.37	0.049	-0.18	0.820	-0.41	0.019
Inferior Temporal	-0.34	0.096	-0.63	1×10^{-5}	-0.27	0.302
Amygdala	-0.62	8×10^{-6}	-0.48	0.003	-0.36	0.065
Hippocampus	-0.60	3×10^{-5}	-0.51	0.001	-0.39	0.035
Parahippocampal	-0.50	0.002	-0.47	0.004	-0.41	0.021
Fusiform	-0.39	0.036	-0.46	0.006	-0.32	0.137
Isthmus of Cingulate	-0.22	0.551	-0.18	0.787	-0.04	1

Table S9 Stepwise linear regression models revealing the contributions of the LIs of control energy (CE) and modal controllability (Mod) in predicting the LI of glucose metabolism (Glu). β values presented here are standardized coefficients.

LI of:	Final model	Statistics for the final model	Statistics for each independent variable
Temporal Pole	Glu ~ β_1×CE	R^2=0.140, F(1,48)=7.810, P=0.007	β_1=-0.374, t=-2.795, P=0.007, VIF=1
Inferior Temporal	Glu ~ β_1×Mod	R^2=0.391, F(1,48)=30.823, P=1×10^{-6}	β_1=-0.625, t=-5.552, P=1×10^{-6}, VIF=1
Amygdala	Glu ~ β_1×CE	R^2=0.385, F(1,48)=29.990, P=2×10^{-6}	β_1=-0.620, t=-5.476, P=2×10^{-6}, VIF=1
Hippocampus	Glu ~ β_1×CE+β_2×Mod	R^2=0.407, F(2,47)=16.151, P=5×10^{-6}	β_1=-0.451, t=-3.382, P=0.001, VIF=1.412 β_2=-0.269, t=-2.018, P=0.049, VIF=1.412
Parahippocampal	Glu ~ β_1×CE	R^2=0.250, F(1,48)=15.973, P=2×10^{-4}	β_1=-0.5, t=-3.997, P=2×10^{-4}, VIF=1
Fusiform	Glu ~ β_1×CE+β_2×Mod	R^2=0.361, F(2,47)=13.280, P=3×10^{-5}	β_1=-0.391, t=-3.349, P=0.002, VIF=1 β_2=-0.459, t=-3.936, P=3×10^{-4}, VIF=1
Isthmus of Cingulate	No variable entered.		

Table S10. Label correspondence between the symmetrically modified Lausanne Atlas and the original Lausanne Atlas (*76*). Each region is assigned to one of the intrinsic connectivity networks (ICNs) (*38*) based on spatial overlap between the Lausanne Atlas and the Schaefer Atlas (*77*).

Original Lausanne Atlas		**Symmetrically modified Lausanne Atlas**		**ICN**
Index	*Region Label*	*Index*	*Region Label*	
1	R_lateralorbitofrontal_1	1	R_lateralorbitofrontal_1	LIM
2	R_lateralorbitofrontal_2	2	R_lateralorbitofrontal_2	LIM
3	R_parsorbitalis_1	3	R_parsorbitalis_1	DMN
4	R_frontalpole_1	4	R_frontalpole_1	LIM
5	R_medialorbitofrontal_1	5	R_medialorbitofrontal_1	DMN
6	R_medialorbitofrontal_2	5	R_medialorbitofrontal_2	DMN
7	R_parstriangularis_1	6	R_parstriangularis_1	DMN
8	R_parsopercularis_1	7	R_parsopercularis_1	SAL/VAN
9	R_rostralmiddlefrontal_1	8	R_rostralmiddlefrontal_1	CONT
10	R_rostralmiddlefrontal_2	9	R_rostralmiddlefrontal_2	CONT
11	R_superiorfrontal_1	10	R_superiorfrontal_1	DMN
12	R_superiorfrontal_2	11	R_superiorfrontal_2	DMN
13	R_superiorfrontal_3	12	R_superiorfrontal_3	SAL/VAN
14	R_superiorfrontal_4	13	R_superiorfrontal_4	DAN
15	R_caudalmiddlefrontal_1	14	R_caudalmiddlefrontal_1	CONT
16	R_precentral_1	15	R_precentral_1	SAL/VAN
17	R_precentral_2	16	R_precentral_2	SMN
18	R_precentral_3	17	R_precentral_3	SMN
19	R_paracentral_1	18	R_paracentral_1	SMN
20	R_rostralanteriorcingulate_1	19	R_rostralanteriorcingulate_1	DMN
21	R_caudalanteriorcingulate_1	20	R_caudalanteriorcingulate_1	SAL/VAN
22	R_posteriorcingulate_1	21	R_posteriorcingulate_1	CONT
23	R_isthmuscingulate_1	22	R_isthmuscingulate_1	DMN
24	R_postcentral_1	23	R_postcentral_1	SMN
25	R_postcentral_2	24	R_postcentral_2	SMN
26	R_supramarginal_1	25	R_supramarginal_1	DAN
27	R_supramarginal_2	26	R_supramarginal_2	SAL/VAN
28	R_superiorparietal_1	27	R_superiorparietal_1	DAN
29	R_superiorparietal_2	28	R_superiorparietal_2	DAN
30	R_superiorparietal_3	29	R_superiorparietal_3	VIS
31	R_inferiorparietal_1	30	R_inferiorparietal_1	DMN
32	R_inferiorparietal_2	30	R_inferiorparietal_2	DMN

33	R_inferiorparietal_3	31	R_inferiorparietal_3	DAN
34	R_precuneus_1	32	R_precuneus_1	DMN
35	R_precuneus_2	33	R_precuneus_2	DMN
36	R_cuneus_1	34	R_cuneus_1	VIS
37	R_pericalcarine_1	35	R_pericalcarine_1	VIS
38	R_lateraloccipital_1	36	R_lateraloccipital_1	VIS
39	R_lateraloccipital_2	37	R_lateraloccipital_2	VIS
40	R_lateraloccipital_3	37	R_lateraloccipital_3	VIS
41	R_lingual_1	38	R_lingual_1	VIS
42	R_lingual_2	39	R_lingual_2	VIS
43	R_fusiform_1	40	R_fusiform_1	VIS
44	R_fusiform_2	41	R_fusiform_2	LIM
45	R_parahippocampal_1	42	R_parahippocampal_1	LIM
46	R_entorhinal_1	43	R_entorhinal_1	LIM
47	R_temporalpole_1	44	R_temporalpole_1	LIM
48	R_inferiortemporal_1	45	R_inferiortemporal_1	LIM
49	R_inferiortemporal_2	46	R_inferiortemporal_2	DAN
50	R_middletemporal_1	47	R_middletemporal_1	DMN
51	R_middletemporal_2	48	R_middletemporal_2	DMN
52	R_bankssts_1	49	R_bankssts_1	SAL/VAN
53	R_superiortemporal_1	50	R_superiortemporal_1	SMN
54	R_superiortemporal_2	51	R_superiortemporal_2	DMN
55	R_transversetemporal_1	52	R_transversetemporal_1	SMN
56	R_insula_1	53	R_insula_1	SMN
57	R_insula_2	54	R_insula_2	SAL/VAN
58	R_thalamusproper	55	R_thalamusproper	SUB
59	R_caudate	56	R_caudate	SUB
60	R_putamen	57	R_putamen	SUB
61	R_pallidum	58	R_pallidum	SUB
62	R_accumbensarea	59	R_accumbensarea	SUB
63	R_hippocampus	60	R_hippocampus	LIM
64	R_amygdala	61	R_amygdala	LIM
65	L_lateralorbitofrontal_1	62	L_lateralorbitofrontal_1	LIM
66	L_lateralorbitofrontal_2	63	L_lateralorbitofrontal_2	LIM
67	L_parsorbitalis_1	64	L_parsorbitalis_1	DMN
68	L_frontalpole_1	65	L_frontalpole_1	LIM
69	L_medialorbitofrontal_1	66	L_medialorbitofrontal_1	DMN
70	L_parstriangularis_1	67	L_parstriangularis_1	DMN
71	L_parsopercularis_1	68	L_parsopercularis_1	SAL/VAN

72	L_rostralmiddlefrontal_1	69	L_rostralmiddlefrontal_1	CONT
73	L_rostralmiddlefrontal_2	69	L_rostralmiddlefrontal_2	CONT
74	L_rostralmiddlefrontal_3	70	L_rostralmiddlefrontal_3	DMN
75	L_superiorfrontal_1	71	L_superiorfrontal_1	DMN
76	L_superiorfrontal_2	72	L_superiorfrontal_2	DMN
77	L_superiorfrontal_3	73	L_superiorfrontal_3	DMN
78	L_superiorfrontal_4	74	L_superiorfrontal_4	SAL/VAN
79	L_caudalmiddlefrontal_1	75	L_caudalmiddlefrontal_1	DAN
80	L_precentral_1	78	L_precentral_1	SMN
81	L_precentral_2	78	L_precentral_2	SMN
82	L_precentral_3	77	L_precentral_3	SMN
83	L_precentral_4	76	L_precentral_4	SAL/VAN
84	L_paracentral_1	79	L_paracentral_1	SMN
85	L_rostralanteriorcingulate_1	80	L_rostralanteriorcingulate_1	DMN
86	L_caudalanteriorcingulate_1	81	L_caudalanteriorcingulate_1	SAL/VAN
87	L_posteriorcingulate_1	82	L_posteriorcingulate_1	CONT
88	L_isthmuscingulate_1	83	L_isthmuscingulate_1	DMN
89	L_postcentral_1	85	L_postcentral_1	SMN
90	L_postcentral_2	85	L_postcentral_2	SMN
91	L_postcentral_3	84	L_postcentral_3	SMN
92	L_supramarginal_1	87	L_supramarginal_1	SAL/VAN
93	L_supramarginal_2	86	L_supramarginal_2	CONT
94	L_superiorparietal_1	88	L_superiorparietal_1	DAN
95	L_superiorparietal_2	89	L_superiorparietal_2	DAN
96	L_superiorparietal_3	90	L_superiorparietal_3	VIS
97	L_inferiorparietal_1	92	L_inferiorparietal_1	DAN
98	L_inferiorparietal_2	91	L_inferiorparietal_2	DMN
99	L_precuneus_1	94	L_precuneus_1	DMN
100	L_precuneus_2	93	L_precuneus_2	DMN
101	L_cuneus_1	95	L_cuneus_1	VIS
102	L_pericalcarine_1	96	L_pericalcarine_1	VIS
103	L_lateraloccipital_1	97	L_lateraloccipital_1	VIS
104	L_lateraloccipital_2	98	L_lateraloccipital_2	VIS
105	L_lingual_1	99	L_lingual_1	VIS
106	L_lingual_2	100	L_lingual_2	VIS
107	L_fusiform_1	101	L_fusiform_1	VIS
108	L_fusiform_2	102	L_fusiform_2	LIM
109	L_parahippocampal_1	103	L_parahippocampal_1	LIM
110	L_entorhinal_1	104	L_entorhinal_1	LIM

111	L_temporalpole_1	105	L_temporalpole_1	LIM
112	L_inferiortemporal_1	106	L_inferiortemporal_1	LIM
113	L_inferiortemporal_2	107	L_inferiortemporal_2	DAN
114	L_middletemporal_1	108	L_middletemporal_1	DMN
115	L_middletemporal_2	109	L_middletemporal_2	DMN
116	L_bankssts_1	110	L_bankssts_1	DMN
117	L_superiortemporal_1	111	L_superiortemporal_1	SMN
118	L_superiortemporal_2	112	L_superiortemporal_2	DMN
119	L_transversetemporal_1	113	L_transversetemporal_1	SMN
120	L_insula_1	114	L_insula_1	SMN
121	L_insula_2	115	L_insula_2	SAL/VAN
122	L_thalamusproper	116	L_thalamusproper	SUB
123	L_caudate	117	L_caudate	SUB
124	L_putamen	118	L_putamen	SUB
125	L_pallidum	119	L_pallidum	SUB
126	L_accumbensarea	120	L_accumbensarea	SUB
127	L_hippocampus	121	L_hippocampus	LIM
128	L_amygdala	122	L_amygdala	LIM
129	brainstem	123	brainstem	Not assigned

* The brainstem is excluded from the analysis due to insufficient coverage in some subjects. Abbreviations: VIS, visual network; SMN, somatomotor network; DAN, dorsal attention network; SAL/VAN, salience/ventral attention network; CONT, executive control network; DMN, default mode network; SUB, subcortical network.

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